REMARKS

Claims 40-42, 45, 47-49, 63 and 64 are pending. Claim 46 stands withdrawn. It is understood that withdrawn claim 46 will be rejoined upon allowance of a linking claim. Applicants respectfully request entry of the amendment, and reconsideration of the pending claims.

Reply to Rejection Under 35 U.S.C. § 112, ¶ 1, Written Description

Claims 37, 40-42, 45, 47-49 and 63-64 were rejected under 35 U.S.C. § 112, ¶ 1 as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, ¶ 1. *See* Office Action at section 4.

The Examiner states that "the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *Id.* In response to Applicants' previous arguments, the Examiner states that "...all the specification has described is an association study between metabolites and HCV, as obtained from HCV infected subjects who are diagnosed with Gaucher's disease or is free of Gaucher's disease" and that "...such is not sufficient to reasonably convey to the skilled artisan in the relevant art that Applicant has possession of the claimed invention." *See* Office Action at page 3.

The Examiner then states that Applicants have not provided adequate written description of glycolipids that treat HCV. *Id.* at page 4. The Examiner contends that there is nothing in the specification to support Applicants' claim that the administration of glycolipids treat HCV. *Id.* at page 5-6. The Examiner then restates her arguments articulated in the prior Office Action. First, the Examiner states that "The specification does not contain a description of **actual reduction to practice** . *Id.* at p. 8. (emphasis added). Second, the Examiner states, "Nor does the specification contain drawings demonstrating that administration of glycolipids treats HCV ." *Id.* at p. 8. (emphasis added). Third, the Examiner states, "The specification does not contain any working examples demonstrating or evidencing that administration of glycolipids treats HCV." *Id.*

Applicants respectfully traverse the examiner's rejection and maintain that subject matter of claims 37, 40-42, 45, 47-49 and 63-64 was described adequately in the specification as filed so as to convey to one of skill in the art that the inventors had possession of the claimed invention.

Initially, Applicants note that claim 37 (and its dependent claims) are directed to "[a] process for treating a disease in a mammalian subject comprising a) obtaining cells from said subject; b) treating said cells with an effective amount of an intermediary metabolite or reagent that increases the intracellular level of a mammalian intermediary metabolite in said cells; and c) transferring said treated cells to said subject, wherein said intermediary metabolite or reagent is a glycolipid, and wherein said disease is cancer, a viral infection, or an autoimmune disease." The specification, as filed, clearly supports this recitation of this process, *inter alia* at page 13, lines 7-15; page 14, lines 5-13; and page 16, line 9 - page 17, line 17. The specification, as filed, elaborates, *e.g.,* on page 15, lines 1-5, that the intermediary metabolite may be a glycolipid, as claimed. The specification *inter alia* at page 15, lines 10-16 and page 16, lines 1-2, also specifies that a viral infection such as HCV (the elected species of the present invention) is among several diseases which may be treated in accordance with the present invention.

The specification further notes at page 1, lines 2-11, that the provided processes for regulation or manipulation of the immune system alter the intracellular or serum levels of intermediate metabolites in a subject and that such manipulation or change in the immune system may be achieved ***directly or indirectly*** (emphasis added). The Examiner's assertion at page 5 of the Office Action that "[a]pplicant has not demonstrated or provided any guidance as to which component of the immune profile must be modulated to treat HCV infection" is misplaced, since the claims do not recite any change in immune components. The claims relate to treatment with "an effective amount of an intermediary metabolite or a reagent that increases the intracellular level of a mammalian intermediary metabolite", **not** to a method of manipulation or change in a ***particular*** immune system component, which itself may alter the intracellular levels of intermediate metabolites. The level of detail required by the Examiner is beyond the scope of the claims, which do not recite an underlying mechanism for the increased level of the mammalian intermediary metabolite or reagent.

The specification at page 7, lines 9-12, describes indirect means of altering the intracellular levels of intermediate metabolites, describing that "immune cells can be treated ex vivo and reintroduced into the subject," as recited by the claims.[1] In addition, the specification describes that "[e]ffective amounts of the [intermediary] metabolite or reagent introduced into the cells ... should depend upon the individual pharmacokinetic properties of said compounds [*i.e.,* the intermediary metabolite or reagent] to achieve sufficient levels of said metabolite in said subject for the duration desired." *See* Specification, page 13, lines 16-19.

Moreover, the specification describes that intermediary metabolites, such as glucosylceramides, may be administered to a subject "such that one component of the immune system is elevated to such an extent that a specific activation of the NKT cell population [a particular component of the immune system] is effected." *See, e.g.,* page 13, line 23 – page 14, line 5. Applicants submit that the specification provides evidence that specific immune parameters are modulated in response to a metabolite, such as a glycolipid. For example, Figures 1-6 illustrate the results of assays leading to T-cell proliferation and changes in IFNγ serum levels, IL-4 serum levels, IL-10 serum levels and peripheral NKT lymphocytes. Thus, Applicants maintain that the specification, as filed, provides a written description for one of skill in the art as to types of immune parameter or marker which may be gauged upon treatment of ex vivo cells with a glycolipid when that particular immune response is part of the pathogenesis of a disease, *e.g.,* T-cells, IFN-gamma, IL-4, IL-10 and peripheral NKT lymphocytes. Therefore, the Examiner's assertion of no investigation having been provided by Applicants as to which immune component has to be changed by glycolipid administration is incorrect.

As noted above, however, the Examiner's requirement that such specific immune component change be shown is misplaced, since the pending claims are directed to a process for treating a disease so as to thereby increase the levels of mammalian intermediary metabolite or reagent, such as a glycolipid. The claims do **not** recite

[1] The specification also describes in detail direct ways to achieve such elevated levels of metabolites (for example, at page 7, lines 8-10).

a method of manipulation or change in a ***particular*** immune system component, which itself may alter the intracellular levels of intermediate metabolites. Accordingly, the level of detail required by the Examiner, *i.e.,* the immune component change, is beyond the scope of the claims, which do not recite an underlying mechanism for the increased level of the mammalian intermediary metabolite or reagent.

Finally, Applicants wish to again direct the Examiner's attention to recent Federal Circuit case law which clarifies what is **not** required for an adequate written description. *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) held that "(1) **examples are not necessary to support the adequacy of a written description** (2) the **written description standard may be met even where actual reduction to practice of an invention is absent**; and (3) **there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.**" (emphasis added).

The Inglis application was directed to poxvirus, but did not contain examples involving the poxviruses. *Id.* The Federal Circuit reiterated that a claim will not be invalidated because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language "because the patent specification is written for a person of skill in the art, and as such a person comes to the patent with the knowledge of what has come before" and "in that context, it is unnecessary to spell out every detail of the invention in the specification..." *Id.* (*citing LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (internal citations omitted)).

The Federal Circuit cited its explanation in *Capon v. Eshar* that "[t]he 'written description' requirement implements the principle that a patent must describe a technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." 418 F.3d 1349, 1357 (Fed. Cir. 2005). Thus, the fact that "Inglis had not actually produced a poxvirus vaccine" was not dispositive, "because an actual reduction to practice is not required for written description." *Id.* at 1366 (*citing Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (not suggesting that written

description can be satisfied only by providing an actual reduction to practice and stating that constructive reduction to practice is an established method of disclosure). *Id.* at 1367. An "'invention' must refer to a concept that is complete, rather than merely one that is "substantially complete.'" *Id.* (*citing Pfaff v. Wells Elecs.*, 525 U.S. 55,66 (1998)).

Accordingly, the Examiner's requirement for the written description requirement at page 9 of the Office Action that the specification provide[s] ... "evidence relating to the effective use of glycolipids to treat HCV infection" and that Applicants must "characterize[] the effect of glycolipids in subjects that are infected with HCV" runs contrary to the *Falkner* holding that examples are not necessary to support the adequacy of a written description. *Falkner*, 448 F.3d at 366.

Second, the Examiner's statement at page 8 of the Office Action that "the specification does not contain a description of actual reduction to practice that glycolipids are effective in treating HCV infection" clearly runs contrary to the *Falkner* holding that "the written description standard may be met even where actual reduction to practice of an invention is absent." *Falkner*, 448 F.3d at 366.

Third, Applicant has provided a constructive reduction to practice, which is an established method of disclosure for written description. Thus, the Examiner's assertion at page 8 that "The specification fails to provide a description of the claimed invention showing that claimed invention is complete, ready for patenting" is erroneous.

Lastly, the Examiner misconstrues the methods of the present invention with the conclusion at page 5 of the Office Action that an HCV infection would resolve itself in a Gaucher patient. The present invention provides for amelioration of symptoms. Applicant's invention has never been described as a cure for this disease.

For these reasons, Applicants submit that the claimed process for "treating a disease in a mammalian subject comprising a) obtaining cells from said subject; b) treating said cells with an effective amount of an intermediary metabolite or reagent that increases the intracellular level of a mammalian intermediary metabolite in said cells; and c) transferring said treated cells to said subject, wherein said intermediary metabolite or reagent is a glycolipid, and wherein said disease is cancer, a viral infection, or an autoimmune disease" is sufficiently described by the specification as filed for a person of skill in the art. Therefore, Applicants respectfully request reconsideration and

withdrawal of the rejection of claims 37, 40-42, 45, 47-49 and 63-64 under 35 U.S.C. § 112, first paragraph for lack of written description.

Reply to Rejection Under 35 U.S.C. § 112, ¶ 1, Enablement

Claims 37, 40-42, 45, 47-49 and 63-64 were rejected under 35 U.S.C. § 112, ¶ 1 as allegedly failing to comply with the enablement requirement.

In considering the *Wands* factor of the nature of the invention is whether the specification would require undue experimentation by one of skill in the art, the Examiner at page 16 states, that the "claimed invention is directed at the treatment of diseases, wherein the elected disease is hepatitis C virus, HCV, with the administration of a glycolipid" and that "the claimed invention relates to the application of glycolipid to regulate and manipulate immune responses, Th1 and Th2 responses, in mammalian subjects..."

With respect to the *Wands* factor of the breadth of the claims, the Examiner at page 16 states that "the claims encompass all diseases...."

Regarding the *Wands* factor of presence or absence of working examples, the Examiner at pages 16-17 avers that "[t]he specification does not contain any working examples demonstrating the effective use of glycolipids to treat HCV infection" and that "Applicant has not set forth any guidance or direction relating to the immune component that must be changed or modulated in order to render treatment to HCV infected subjects."

As to the *Wands* factor of the state of the art, the Examiner at page 17 states that "[t]he hepatitis C virus (HCV) art clearly notes that the role of innate and antigen-nonspecific response to HCV has not yet been sufficiently characterized" and that in such absence, "the skilled artisan would not readily be able to practice the claimed invention without an undue burden of experimentation." It should be noted that the present invention does not depend upon a characterization of the mechanism by which an immune response to HCV contributes to the pathogenesis of the disease and only seeks to reduce the effects caused by this response. The Examiner asserts at page 18 that several factors challenge the development of an effective treatment for HCV, including 1) the

lack of an effective cell culture system, 2) "the absence of good animal models, outside of humans and chimpanzees," and 3) "the ability of HCV to evade effective immune recognition, including recognition by cytotoxic T lymphocytes (CTL) and shows an extremely high rate of viral persistence." The Examiner further asserts that the last enumerated factor "establishes that the type of experimentation that the skilled artisan would have to perform ... is beyond routine experimentation, such as establishing route of administration and treatment dosage amounts." *See* Office Action, page 18.

Regarding the *Wands* factor of quantity of experimentation necessary, the Examiner states on page 19 that "[i]n order for the skilled artisan to successfully practice the claimed invention, the skilled artisan would have to blindly and unduly experiment with glycolipids, each immune component and determine the relationship among the glycolipids, each immune component and HCV infection." While the specification discloses that the dosage effects of a glycolipid on one or more immune properties would be known to be associated with a disease (such as HCV), the Examiner seems to believe that there would be a further requirement for establishing the exact relationship (mechanism) between glycolipids, immune components and HCV. While this research into the mechanism would certainly be of continued interest to a researcher, it is not required for the practice of the present invention.

Applicants respectfully disagree and traverse this rejection and maintain that the specification offers adequate guidance to those skilled in the art to practice the claimed process of claims 37, 40-42, 45, 47-49 and 63-64.

It is well established under 35 U.S.C. §112 ¶ 1, that, "[t]he test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is *undue*." MPEP 2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976) (Emphasis added). Applicants maintain that the specification provides sufficient guidance to enable one skilled in the art to treat a disease in a mammalian subject by obtaining cells from the patient, treating the cells with an effective amount of an intermediary metabolite and transferring the treated cells to the subject, to increase the intracellular level of a mammalian intermediary metabolite in said subject, as claimed.

Applicants address the *Wands* factors in turn.

Nature of the Invention

As discussed above in the discussion of written description, claim 37 and its dependent claims relate or are directed to "[a] process for treating a disease in a mammalian subject comprising a) obtaining cells from said subject; b) treating said cells with an effective amount of an intermediary metabolite or reagent that increases the intracellular level of a mammalian intermediary metabolite in said cells; and c) transferring said treated cells to said subject, wherein said intermediary metabolite or reagent is a glycolipid, and wherein said disease is cancer, a viral infection, or an autoimmune disease," **not** to a method of manipulation or change in a ***particular*** immune system component, which itself may alter the intracellular levels of intermediate metabolites. The specification, as filed, provides, *e.g.,* on page 15, lines 1-5, that the intermediary metabolite may be a glycolipid, as claimed.

Thus, Examiner's statement that the invention relates to regulation and manipulation of immune responses and Th1 and Th2 responses is attempting to insert into the claims a possible underlying mechanism of increasing intracellular or extracellular or serum level of a mammalian intermediary metabolite, however, no such mechanism is specifically recited in the pending claims. Thus, the assertion extends beyond the scope of the **claimed** invention.

Breadth of the Claims

Applicants maintain that the Examiner's assertion that the "claims encompass all diseases ... " is over-inclusive. In fact, the claim 37 recites diseases such as cancer, a viral infection or an autoimmune disease. HCV is the elected species of a viral infection of the present invention.

Presence or Absence of Working Examples

As noted above, the Examiner's requirement of examples of or guidance for which immune components must be changed or modulated in order to render treatment to HCV infected subjects is misplaced. The claims are directed to a process for treating a disease, **not** to a method of manipulation or change in a ***particular*** immune system

component, which itself may alter the intracellular or serum levels of intermediate metabolites.

The specification at page 7, lines 9-12, describes indirect means of altering the intracellular levels of intermediate metabolites, reading that "immune cells can be treated ex vivo and reintroduced into the subject," as recited by the claims. In addition, the specification describes that "[e]ffective amounts of the [intermediary] metabolite or reagent introduced into the cells ... should depend upon the individual pharmacokinetic properties of said compounds [*i.e.,* the intermediary metabolite or reagent] to achieve sufficient levels of said metabolite in said subject for the duration desired." *See* Specification, page 13, lines 16-19.

Further, the specification *inter alia* at page 15, lines 10-16 and page 16, lines 1-2, also specifies that a viral infection such as HCV (the elected species of the present invention) is among several diseases which may be treated in accordance with the present invention.

Applicants note that the level of skill of the relevant artisan is high, *e.g.,* a person having an advanced degree (doctorate or medical degree) in immunology or infectious disease and the like.

Moreover, as the Federal Circuit held in *Falkner*, a claim will not be invalidated because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language "because the patent specification is written for a person of skill in the art, and as such a person comes to the patent with the knowledge of what has come before" and "in that context, it is unnecessary to spell out every detail of the invention in the specification..." *Id.* (*citing LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (internal citations omitted)). *See also* MPEP § 2164.02. (the absence of working examples will not by itself render the invention non-enabled.)

In light of the above discussion, it is clear that the specification sufficiently guides one of skill in the art so as to enable the skilled artisan to treat a disease in a mammalian subject by obtaining and treating cells from the subject with an effective amount of an intermediary metabolite, then returning the cells back to the subject, to increase the intracellular level of a mammalian intermediary metabolite in said subject, as claimed.

State of the Art

The claims are directed to a process for treating a disease, **not** to a method of manipulation or change in a ***particular*** immune system component, which itself may alter the intracellular or serum levels of intermediate metabolites. Therefore, the presently pending claims do not recite a mechanism for a specified "role of innate and antigen-nonspecific response to HCV" or to any specific immune component that is changed upon administration of a mammalian intermediary metabolite or reagent, such as a glycolipid. The Examiner improperly appears to require elucidation of an underlying mechanism for the claimed treatment. The test under 35 U.S.C. §112 ¶ 1, is not "whether any experimentation is necessary, but whether, if experimentation is necessary, it is *undue*." MPEP 2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976) (Emphasis added).

Applicants maintain that the specification provides sufficient guidance to enable one skilled in the art to practice the claimed process of obtaining and treating cells from the subject with an effective amount of an intermediary metabolite, then returning the cells back to the subject, to increase the intracellular level of a mammalian intermediary metabolite in said subject.

The specification teaches one of skill that intermediary metabolites, such as glucosylceramides, may be administered to a subject "such that one component of the immune system is elevated to such an extent that a specific activation of the NKT cell population [a particular component of the immune system] is effected." *See, e.g.,* page 13, line 23 – page 14, line 5. Applicants submit that the specification provides adequate guidance as to specific immune parameters that may be modulated in response to the administration of a intermediary metabolite, such as a glycolipid. For example, Figures 1-6 illustrate the results of assays leading to T-cell proliferation and changes in IFNγ serum levels, IL-4 serum levels, IL-10 serum levels and peripheral NKT lymphocytes. Accordingly, one of skill in the art is guided as to types of immune parameters or markers which may be gauged upon administration of a glycolipid when that particular immune response is part of the pathogenesis of a disease, *e.g.,* T-cells, IFN-gamma, IL-4, IL-10 and peripheral NKT lymphocytes.

Additionally, the specification provides as follows:

> These assays and figures demonstrate that the presence of an increased level of a metabolite has led to significant changes in the immune profile of these subjects. Surprisingly, when this condition was accompanied by another immune system challenge (HCV infection), there was significant impact on the immune profile of the HCV + subjects compared to the subjects that lacked elevation of the metabolite.

See Specification at page 12, first full paragraph.

Applicants again reiterate, that the claims are directed to a method of treatment of a disease by treatment of a patient's cells with an intermediary metabolite or reagent, and do not specify an underlying mechanism of any particular immune component in the amelioration of the disease. Thus, Applicants maintain that the specification, as filed, enables one of skill in the art how to practice the claimed invention without undue experimentation.

Quantity of Experimentation Necessary

Contrary to the Examiner's assertion that one of skill in the art cannot rely on the specification to reasonably practice the invention without undue experimentation, one of skill in the art is adequately guided and enabled to practice the claimed method of treatment of a disease (such as HCV) by treatment of a patient's cells with an intermediary metabolite or reagent, such as a glycolipid. The specification, as filed, provides an association between an increase in the intracellular levels of a mammalian intermediary metabolite or reagent, such as a glycolipid, and the treatment of a disease, such as HCV.

Moreover, the specification clearly set forth a protocol for treating a disease by treatment of a patient's cells with an intermediary metabolite or reagent to increase the intracellular level of the mammalian metabolite. The specification *inter alia* at page 13, lines 7-15; page 14, lines 5-13; and page 16, line 9 - page 17, line 17 describes various means of treating the patient cells and reintroducing the cells back to the subject.

The specification also describes that "[e]ffective amounts of the [intermediary] metabolite or reagent introduced into the cells ... should depend upon the individual

pharmacokinetic properties of said compounds [*i.e.*, the intermediary metabolite or reagent] to achieve sufficient levels of said metabolite in said subject for the duration desired." *See* Specification, page 13, lines 16-19.

Given the high level of skill in the art, the breadth of the claims, the amount of direction and guidance presented in the specification -- such that experimentation by one of skill in the art is not undue, the presently pending claims are fully enabled by the specification as filed.

For the reasons above, Applicants respectfully submit that the pending claims are enabled by the instant specification, and as such, a skilled artisan is sufficiently guided to make and use the claimed invention commensurate with the scope of the presently amended claims without undue experimentation. Applicant respectfully requests reconsideration and withdrawal of this rejection of claims 37, 40-42, 45, 47-49 and 63-64 under 35 U.S.C. § 112, first paragraph for lack of enablement.

In view of at least the foregoing, Applicants respectfully submit that the claims are in condition for allowance.

CONCLUSION

Early notification of a favorable consideration is respectfully requested. The Examiner is respectfully requested to contact the undersigned by telephone at the below listed telephone number, in order to expedite resolution of any issues and to expedite passage of the present application to issue, if any comments, questions, or suggestions arise in connection with the present application.

Respectfully submitted,

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Dated: 3/11/08

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